theory. This amendment adds no new matter and is supported throughout the application, *e.g.,* page 27, lines 14-17.

Claim 34 has been amended to recite that binding to the first or the second site is stored binary information. This amendment adds no new matter and is supported throughout the application.

For convenience, the Examiner's rejections are addressed in the order presented in the Office Action mailed June 19, 2001.

1. The invention

The current invention provides nucleic acid and binding proteins that function as components of molecular logic systems, which operate analogously to electronic logic systems. The central operational element of the molecular logic system is a nucleic acid having at least two protein binding sites that are arranged such that when the first protein binding site is specifically bound by a protein, the second binding site cannot be bound by a protein (that would otherwise specifically bind to the second binding site), and vice versa. The binding sites are therefore mutually exclusive. This characteristic provides a two-state element (a protein is either bound to the first site or to the second site) that is analogous to an electronic component of a digital system. The nucleic acid/binding protein system can thereby act as a static or dynamic data storage element, and further, can act as a logic gate. The stored information is essentially the binding of a protein to the different sites.

2. Species election

Applicants thank the Examiner for withdrawing the species election requirement applied to SEQ ID NO:1-3, which include the same protein binding site.

The Office Action also makes final the species election requirement for species A, drawn to a nucleic acid with two protein binding sites; and species B, drawn to a nucleic acid with three protein binding sites. Applicant note that with regard to this action, it is Applicants understanding that upon the determination that the elected species

is free of the prior art, additional species will be examined in accordance with MPEP § 803.02, which states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." and that "The prior art search will be extended to the extent necessary to determine the patentability of the Markush-type claim."

3. Specification

The Office Action objected to the specification for not containing an abstract on a separate sheet; for referring to Figures 8a, 8b, and 8c, when only Figure 8 was provided, and for inclusion of an embedded hyperlink.

Applicants have provided the requested Abstract, included in Appendix C.

Applicants have submitted a substitute sheet 8 in accordance with the Examiner's suggestion.

The Office Action alleges that browser-executable code is present in the specification at page 7 and elsewhere. Applicants have removed the embedded hyperlink at page 7, but did not note the presence of additional executable codes in the specification. Applicants respectfully request that the Examiner point out the other passages in the specification that include executable code.

4. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-11, 13-14, 34-42, and 44-63 were rejected as allegedly indefinite in the recitation of a number of terms. The rejection is traversed in part and obviated in part by amendments to the claims.

The rejections alleges that the term "encodes" in claims 1, 15, 34, and 51 is unclear. Although Applicants disagree with the Examiner, in order to expedite prosecution, claims 1, 15, 34, and 51 have been amended to recite a nucleic acid that "comprises" the protein binding sites. Applicants therefore respectfully request withdrawal of the rejection.

Claims 2-11, 13-14, and 63 were rejected as allegedly lacking proper antecedent basis for the term "composition". The rejection is obviated in view of the amendment to the claims.

The rejection also alleges that the phrase "the difference in strength" in claims 11, 42, and 61 lacks clear antecedent bases. Applicants submit that the claims are clear. However, in order to expedite prosecution, the claims have been amended to recite "a difference in strength between said first protein binding site and said second protein binding site of more than 0 bits as determined by individual information theory". Applicants therefore request withdrawal of the rejection.

Claims 34 and 51 were rejected as allegedly unclear with regard to the preamble language relating to the storage of information. The rejection alleges that it is not clear from the claim language what constitutes the information and where it is stored. The rejection is traversed in part. The language of the claims is clear, particularly in view of the disclosure in the specification. As noted on page 14, line 29, bridging to page 15, line 11, the systems and compositions of this invention have a nucleic acid with at least two mutually exclusive binding sites. Therefore, (for two binding sites) there are three discrete states: a nucleic acid with no protein bound to it; a nucleic acid with a protein bound to the first site, and a nucleic acid with a protein bound to a second site. For binary storage (typical of digital storage systems) only two states are used, which could be bound nucleic acid versus unbound, or site one bound versus site two bound. Claim 34 recites that a protein is bound to the first or second site. Binding to the first or second site is the stored binary information. Similarly, with regard to claim 51, binding to the first site can be the stored information. Thus, the plain meaning of the words provide ample clarity. Applicants therefore respectfully request withdrawal of the rejection.

5. Rejections under 35 U.S.C. § 103

Claims 1-11, 13, 14, 34-42, and 44-63 were rejected as allegedly unpatentable over Darnell *et al.* in view of Hengen *et al.* Hengen *et al.* describe an oligonucleotide with Fis binding sites that are 11 base pairs apart and 7 base pairs apart

and a protein Fis, that specifically binding to the binding sites. The rejection alleges that Darnell provides a motivation to study DNA binding proteins and their respective binding sites and that it would have been therefore obvious to synthesize artificial nucleic acids containing different Fis sites with different spacing to test their binding to the Fis protein. Applicants respectfully traverse.

In order to expedite prosecution, submitted herewith is an unsigned Declaration of Inventorship under 37 C.F.R. § 132 that removes the publication as a reference. A signed copy of the Declaration will be submitted in a Supplemental Response once both of the inventors' signatures have been obtained.

A 35 U.S.C. 103 rejection is based on the 35 U.S.C. 102(a), 102(b), 103(e), etc. depending on the type of prior art reference used (*see,* MPEP § 2141.01 (I.)). Accordingly, an obviousness rejection based on a publication that would be applied under 102(a) if it anticipated the claims can be overcome by swearing behind the reference, or providing a Declaration that Applicants are the inventors (*e.g.*, MPEP § 715.01(c)). Submitted herewith is a Declaration under 37 C.F.R. § 132 by Thomas Schneider and Paul Hengen, which states that, to the extent the current invention is disclosed in Hengen *et al.*, Applicants are the inventors of the subject matter relating to the claimed invention. The instant application is a 35 U.S.C. § 371 national phase filing of PCT application PCT/US99/03469, filed February 17, 1999, which claims priority to U.S.S.N. 60/075,468, filed February 20, 1998. Hengen *et al.* was published in *Nucl. Acids Res.* 1997 Dec 15;25(24):4994-5002. Accordingly, Hengen *et al.* is not available as a prior art reference.

Even if Hengen *et al.* was available as prior art, Applicants note that the rejection fails to establish a proper case of *prima facie* obviousness, *i.e.,* the rejection fails to show a motivation to modify the prior art to arrive at the claimed invention. While it is interesting to study DNA binding proteins--thousands of research articles have been written on the subject—the rejection fails to point to a principle known in the art that would motivate the skilled artisan to either develop *de novo* oligonucleotides with protein

binding sites that are mutually exclusive, or to modify existing binding elements to achieve this property.

Hengen *et al.* includes no suggestion that the oligonucleotides used to study Fis binding have the binding properties set forth in the claims. Indeed, the gel shift assay on page 5001 (Figure 7) indicates that the two closely-spaced Fis binding elements have very disproportionate binding strengths. The wildtype oligonucleotide would therefore not necessarily be expected to have the property of mutually exclusive binding, as binding to the weak site may not preclude binding to the strong site. Although Darnell *et al.* may provide a motivation to generally study DNA-protein binding interactions, no principle is provided that suggests modifying a wildtype Fis oligonucleotide to have this property. Accordingly, the rejection fails to establish a *prima facie* case of obviousness.

In view of the foregoing, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendment to the paragraph on page 7, lines 1-12:

The term "nucleic acid binding protein" is used herein to refer to a protein that specifically binds to a nucleic acid at a particular nucleotide sequence. Nucleic acid binding proteins include DNA binding proteins, mRNA binding proteins, tRNA binding proteins, and proteins that specifically bind modified or otherwise non-standard nucleic acids as described above. Nucleic acid binding proteins include, but are not limited to DNA binding proteins such as Fis, LacI, lambda cI, lambda cro, LexA, TrpR, ArgR, AraC, CRP, FNR, OxyR, IHF, GalR, MalT, LRP, SoxR, SoxS, sigma factors, chi, T4 MotA, P1 RepA, p53, NF-kappa-B, and RNA binding proteins or protein/RNA complexes such as ribosomes, T4 regA, spliceosomes (donor and acceptor), polyA binding factor, and the like. A large number of nucleic acid binding proteins are described in the TransFac database [(ftp://transfac.gbf-braunschweig.de/pu/transfac/ascii/], *see also Nucleic Acids Res.* (25)(1)265-268 (1997) [ )].

Amendments to the claims:

1. (amended) A system comprising

an isolated nucleic acid having a length of at least 5 base pairs and having a nucleotide sequence that comprises [encodes] a first protein binding site and a second protein binding site where said first and second protein binding sites are spaced in proximity to each other such that:

when said first protein binding site is specifically bound by a protein, said second binding site cannot be bound by a protein that otherwise specifically recognizes and binds said second binding site; and

when said second binding site is specifically bound by a protein, said first binding site cannot be bound by a protein that otherwise specifically recognizes and binds said first binding site; and

a nucleic acid binding protein that specifically binds said first protein binding site or said second protein binding site.

2. (amended) The [composition] system of claim 1, wherein said nucleic acid is a double-stranded nucleic acid.

3. (amended) The [composition] system of claim 1, wherein said nucleic acid is a deoxyribonucleic acid (DNA).

4. (amended) The [composition] system of claim 1, wherein said first binding site and said second binding site have the same nucleotide sequence.

5. (amended) The [composition] system of claim 1, wherein said first binding site and said second binding site have the nucleotide sequence of SEQ ID NO: 1.

6. (amended) The [composition] system of claim 1, wherein said first binding site or said second binding site is specifically recognized and bound by a protein selected from the group consisting of Fis, and Tus.

7. (amended) The [composition] system of claim 1, wherein said first binding site or said second binding site is bound by EF-tu.

8. (amended) The [composition] system of claim 1, wherein said first binding site is within 20 nucleotides of said second binding site.

9. (amended) The [composition] system of claim 1, wherein said first binding site is within 11 nucleotides of said second binding site.

10. (amended) The [composition] system of claim 8, wherein said first binding site has a strength of at least 2.4 bits as determined by individual information theory.

11. (amended) The [composition] system of claim 1, wherein [the] there is a difference in strength between said first protein binding site and said second protein binding site [is at least] of more than 0 bits as determined by individual information theory.

13. (amended) The [composition] system of claim 1, wherein:
said first protein binding site is a Fis binding site;
said second protein binding site is a Fis binding site; and
said binding sites are separated from each other by less than 12 nucleotide base pairs.

14. (amended) The [composition] system of claim 13, wherein said nucleic acid is a deoxyribonucleic acid comprising the sequence of SEQ ID NO: 2 or SEQ ID NO: 3.

15. (amended; drawn to a non-elected species) A composition comprising, an isolated nucleic acid having a length of at least 5 base pairs and having a nucleotide sequence that comprises [encodes] a first protein binding site, a second protein binding site, and a third protein binding site where said protein binding sites are spaced in proximity to each other such that:

when either said first protein binding site or said third protein binding is specifically bound by a nucleic acid binding protein, said second binding site cannot be

bound by a nucleic acid binding protein that otherwise specifically recognizes and binds said second binding site; and

where said first protein binding site and said third protein binding site can simultaneously be specifically bound by a nucleic acid binding protein.

34. (amended) A composition for the storage of binary information, said composition comprising an isolated nucleic acid having a length of at least 3 base pairs and having a nucleotide sequence that comprises [encodes] a first protein binding site and a second protein binding site where said first and second protein binding sites are spaced in proximity to each other such that:

when said first protein binding site is specifically bound by a protein, said second binding site cannot be bound by a protein that otherwise specifically recognizes and binds said second binding site; and

when said second binding site is specifically bound by a protein, said first binding site cannot be bound by a protein that otherwise specifically recognizes and binds said first binding site; and

further comprising a nucleic acid binding protein bound to said. first protein binding site or said second protein binding site.

42. (amended) The composition of claim 34, wherein [the] there is a difference in strength between said first protein binding site and said second protein binding site [is at least] of more than 0 bits as determined by individual information theory.

51. (amended) A method of storing information, said method comprising the step of:

binding a nucleic acid binding protein to a first protein binding site on a nucleic acid, wherein said nucleic acid has a length of at least 3 base pairs and said nucleic acid comprises [encodes] said first protein binding site and a second protein

binding site where said first and second protein binding sites are spaced in proximity to each other such that:

when said first protein binding site is specifically bound by a protein, said second binding site cannot be bound by a protein that otherwise specifically recognizes and binds said second binding site; and

when said second binding site is specifically bound by a protein, said first binding site cannot be bound by a protein that otherwise specifically recognizes and binds said first binding site.

61. (amended) The method of claim 51, wherein [the] there is a difference in strength between said first protein binding site and said second protein binding site [is at least] of more than 0 bits as determined by individual information theory.

63. (amended) The [composition] system of claim 13, wherein said nucleic acid is a deoxyribonucleic acid comprising the sequence of SEQ ID NO: 2 or SEQ ID NO: 3.